"Design, Synthesis and Investigation of Potential Pharmacophores derived from Hybrid based Heterocycles"

A synopsis submitted to

Swami Ramanand Teerth Marathwada University,
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1.Introduction:

Heterocyclic chemistry is one of the most complex and intriguing branches .Study of heterocyclic chemistry is evergreen branch of organic chemistry.Nearly two thirds of organic compounds are heterocyclic compounds. A cyclic organic compound containing all carbon atoms in a ring formation is referred to as carbocyclic compound. If at least one atom other than carbon forms a part of the ring system, then it is designated as heterocyclic compound. Nitrogen, oxygen and sulphur are the most common hetero atoms, but heterocyclic rings containing other hetero atoms are also widely known.An enormous number of heterocyclic compounds are known and this number is increasing rapidly.

Heterocyclic compounds bearing –SH, NH, N-C-S, NH-R and N-C=S, groups in a ring have an important role in organic synthesis and medicinal chemistry due to their considerable bioactivity. It makes possible research, upgrading the synthesis, modification and changes in structure of heterocyclic compounds. The compounds are also accompanied by changing the biological activity. Many naturally occurring and synthetic compounds containing Nitrogen, Sulfur and Oxygen elements possess interesting pharmacological properties. They are continuing to be in the focus of life science-oriented research.

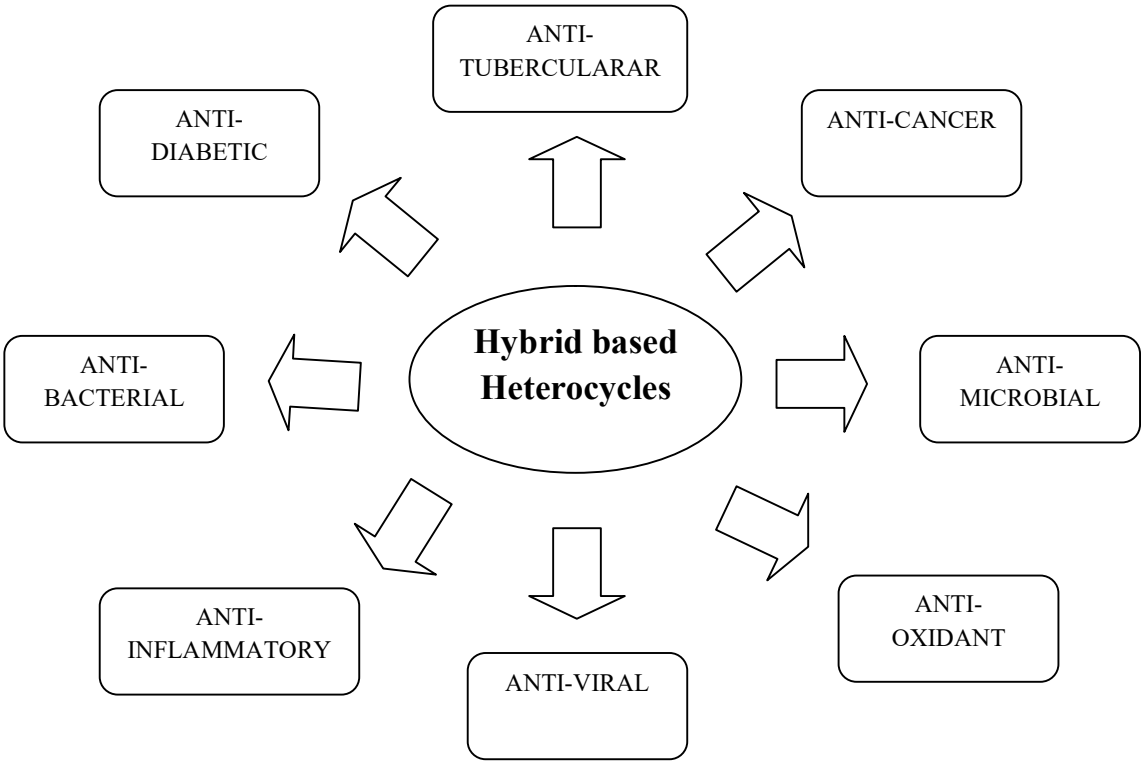
The remarkable ability of heterocyclic nuclei to serve both as bioimmetics and reactive pharmacophores has largely contributed to their unique values as traditional key elements in numerous drugs.The development of heterocycles scaffolds containing a high degree of diversity has become a leading focus in modern drug discovery.

By addition of diverse substituents certain possible modifications on the heterocycle may lead to new products with better biological profiles. As a result of the biological activity exhibited by the heterocyclic molecules,the development of new chemical entities (NCEs) is the focus of intense activity in pharamaceutical industry .Variety of newly synthesized molecules may be very good at blocking the action or killing the bacteria without harming human cells so as to prevent or cure the disease .The main aim of heterocycles study is to synthesize and design molecules involving the use of structural motif commonly found in majority of well established drug molecules.

Hence we aimed to study and development of new heterocyclic derivatives by using structural modification strategy, molecular hybridization (MH) or hybrid based heterocyclic.

Design of new drugs with better physicochemical properties, adequate absorption, distribution, metabolism, and excretion along with effective pharmacologic potency and lack of toxicity for the treatment of infectious diseases has suffered a continuous decrease.

So the development of such molecular frameworks with synthetic and economic accessibility, still represent a big challenge for the pharmaceutical sector and demands continuous efforts .An emerging strategy within medicinal chemistry and drug discovery is the combination of two distinct pharmacophores into a single molecule,well documented as molecular hybridization (MH) or hybrid based molecules (here hybrid based heterocyclic molecule).



MH is a structural modification strategy useful in the designing of new optimized ligands and prototypes with new molecular architectures composed of two or more bioactive derivatives, through the adequate fusion of these subunits.

2. Review of Literature and Development in the subject:

After a literature survey to the best of our knowledge showed that hybrid based heterocycles and their analogues have important and wide application in organic chemistry, medicinal chemistry and pharmaceutical industries. Combinations of adequate subunits through the molecular hybridization, can create new entities with better biological profiles.

Some hybrid based heterocycles showing their broad spectrum applications such as:

Name	Parent Nuclei	Biological Activity
Aminocoumarin	Coumarin	Antibiotic
Warfarin	Coumarin	Anticoagulant
Batoprazine	Coumarin	Anti-aggressive agent
Dacomitinib	Quinazoline	To treat cancer
Vendetanib	Quinazoline	Drug against medullary thyroid cancer
Granisoton	Pyrazole	Antagonist
Nesapidil	Oxadiazole	Anti-arrhethmic

By literature review of various hybrid based heterocycles, it was found that they have very much attention at the national and international level.

3. Objective of research / Proposed Hypothesis:

The objective of the research work is boosting our interest in designing, synthesis and investigation of potential pharmacophores derived from hybrid based heterocycles.Thus the potential hybrid based heterocycles are having wide applications in pharmaceutical industries. Keeping this in mind, the objectives will be synthesis of various substituted hybrid based heterocycles and investigation of their applications in various fields.

4. Methodology to be adopted:

Numerous preparative methods of organic synthesis will have been used in our work. The isolation and purification of crude products and separation of isomer will carry out by the crystallization and column chromatography. The obtained products will be identified and characterized by elemental analysis, Meltimg Point determination ^{1}H NMR, ^{13}CNMR, MASS and IR techniques.

5.Importance of study /society applications:

Significance of the study:

The molecular hybridization strategy is particularly interesting for the development of the treatment of physicopathologies where treatment is restricted to fewer commercial drugs or in cases when bioactive compounds are discovered but present high toxicity or or pharmacokinetic and pharmacodynamic restrictions.

Combinations of adequate subunits through the molecular hybridization, can create new entities with better biological profiles.The significance or advantage of using molecular hybridization is to activate different targets by a single molecule, thereby increasing therapeutic efficiency as well as to improve the bioavailability.

Hybrid based heterocycles containing molecules currently used in clinical medicine at the **national** and **international** level are like *raltegravir* an antiretroviral drug for the treatment of HIV infection, *furamizole* a nitrofuran derivative that has strong antibacterial activity, *ataluren* for treatment of cystic fibrosis and *tiodazosin* an antihypertensive drug contain the oxadiazole nucleus.

Afatinib act as potential therapeutics for solid tumors, including nonsmall cell lung cancer, *Barasertib* act as an aurora kinase inhibitor for the treatment of acute myeloid leukemia, *Doxazosin* act as antihypertensive agent and *Alfuzosin* used to treat prostatic hyperplasia, all these drugs are containing quinazoline nucleus in a hybrid form.In addition to this, there are many well known significant drugs and medicines containing various hybrid based heterocycles.

The potential significance of hybrid based heterocycles has been growing interest in the scientific community and motivated to opportunity for my research work.

With the given background and motivation, I would like to focus on hybrid based heterocycles and their derivatives have significant and potential application in various fields.

6. Proposed work plan /Formulation of structured study:

Year wise plan of work and targets to be achieved :

Plan	First Year	Second Year	Third Year
Literature Survey			
Design and Molecular modeling			
Synthesis and Characterization			
Biological study			
Outcome of Research			

Research Plan

First Year

1. Literature survey on Hybrid based Heterocycles.
2. Design of new potent molecules .
3. Molecular modeling studes of new molecules.

Second Year

4. Synthesis of new Hybrid based heterocycles using green approach.
5. Structural characterization of newly synthesized molecules using spectroscopic methods.

Third Year

6. Biological study of Hybrid based Heterocycles.
7. Studies on Structure Activity Relationship.
8. Outcome of Research.

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